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Health and Environmental Effects Profile for Tetra-, Penta- and Hexachlorodibenzofurans

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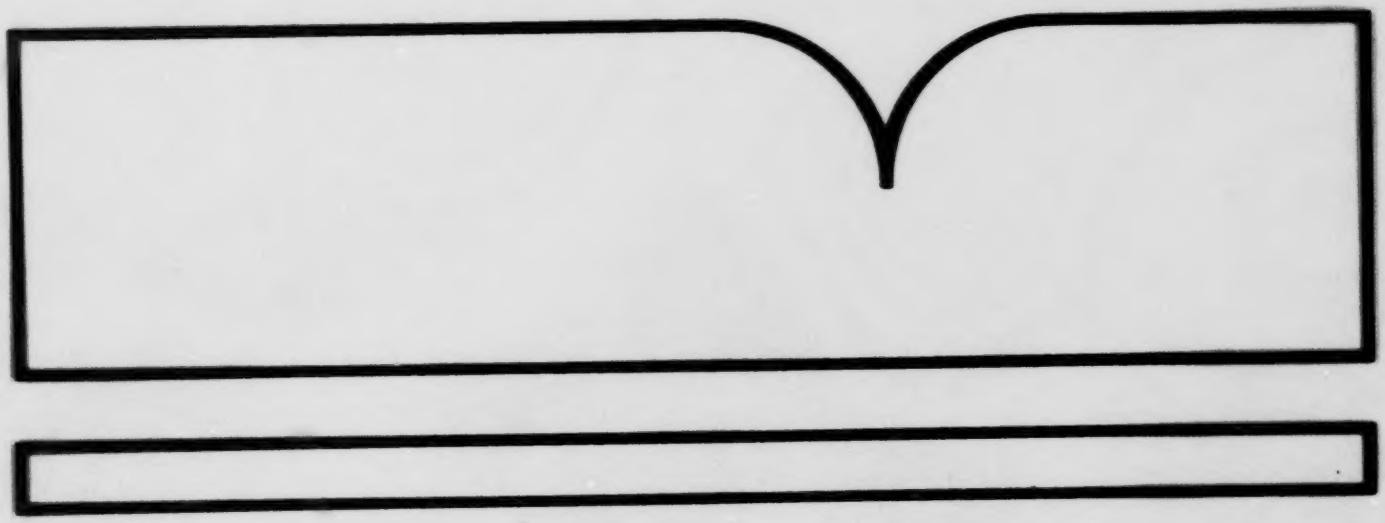

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR TETRA-,PENTA- AND HEXACHLORODIBENZOFURANS

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16. ABSTRACT

The Health and Environmental Effects Profile for Tetra-,Penta-and Hexachlorodibenzofurans was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic factor for Tetra-,Penta- and Hexachlorodibenzofurans.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1-1
1.1.	PHYSICAL PROPERTIES	1-1
1.2.	CHEMICAL PROPERTIES	1-1
1.3.	SYNTHESIS	1-3
1.4.	SOURCES IN THE ENVIRONMENT	1-3
1.5.	USES	1-4
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	2-1
2.1.	AIR, WATER AND SOIL	2-1
2.2.	BIOACCUMULATION	2-1
3.	EXPOSURE	3-1
3.1.	WATER	3-1
3.2.	FOOD	3-1
3.3.	AIR	3-2
3.4.	DERMAL	3-3
4.	PHARMACOKINETICS	4-1
4.1.	ABSORPTION	4-1
4.2.	DISTRIBUTION	4-1
4.3.	METABOLISM	4-3
4.4.	EXCRETION	4-4
5.	EFFECTS	5-1
5.1.	CARCINOGENICITY	5-1
5.2.	MUTAGENICITY	5-2
5.3.	TERATOGENICITY	5-2
5.4.	OTHER REPRODUCTIVE EFFECTS	5-3
5.5.	CHRONIC TOXICITY -- HUMANS	5-3
5.6.	ACUTE	5-10
5.7.	OTHER RELEVANT INFORMATION	5-12
6.	AQUATIC TOXICITY	6-1
6.1.	ACUTE	6-1
6.2.	CHRONIC	6-1
6.3.	PLANT EFFECTS	6-2
6.4.	RESIDUES	6-2
6.5.	OTHER RELEVANT INFORMATION	6-3
7.	EXISTING GUIDELINES AND STANDARDS	7-1
8.	REFERENCES	8-1

LIST OF TABLES

No.	Title	Page
1-1	Physical Properties of Dibenzofuran and a Few Selected Substituted Dibenzofurans	1-2
5-1	Symptoms of "Yusho" Disease in 89 Male and 100 Female Patients.	5-5
5-2	Relation Between the Amount of the Rice Oil Used by "Yusho" Patients, Amounts of PCB and PCDF Ingested, and Clinical Severity	5-6
5-3	Subchronic Toxicity of Polychlorinated Dibenzofurans.	5-9
5-4	Summary of Pathologic Effects of 2,3,7,8-Tetra-CDBF in Rhesus Monkeys.	5-13
5-5	Acute Oral Toxicity of Polychlorinated Dibenzofurans and 2,3,7,8-Tetra-CDD	5-14

LIST OF ABBREVIATIONS

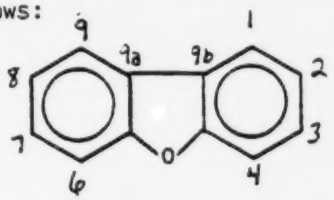
ADI	Acceptable daily intake
BCF	Bioconcentration factor
BDBF	Bromodibenzofuran
BUN	Blood urea-nitrogen
bw	Body weight
CDD	Chlorodibenzo-p-dioxin
CDF	Chlorodibenzofuran
CDBF	Chlorinated dibenzofurans
CNRC	Canadian National Research Council
DBF	Dibenzofuran
FDA	Food and Drug Administration
FEL	Frank effect level
IARC	International Agency for Research on Cancer
i.p.	Intraperitoneal
i.v.	Intravenous
LOAEL	Low-observed-adverse-effect level
NAS	National Academy of Sciences
NIEHS	National Institute of Environmental Health Services
NOAEL	No-observed-adverse-effect level
NRCC	National Research Council of Canada
NTIS	National Technical Information Service
OCDF	Octachlorodibenzofuran
PCB	Polychlorinated biphenyl
PCDD	Polychlorinated dibenzo-p-dioxin
PCDF	Polychlorinated dibenzofuran

s.c.	Subcutaneous
SGOT	Serum glutamic oxaloacetic transaminase
2,4,5-T	2,4,5-Trichlorophenoxyacetic acid
TCDD	Tetrachlorodibenzo-p-dioxin
TCDF	Tetrachlorodibenzofuran
WHO	World Health Organization

1. INTRODUCTION

1.1. PHYSICAL PROPERTIES

The DBFs are a group of organic compounds that contain the dibenzofuran moiety. The structure of DBF and the accepted system of numbering the ring substitutions are as follows:



There are 135 positional isomers for a single substituent: 4 mono-, 16 di-, 28 tri-, 38 tetra-, 28 penta-, 16 hexa-, 4 hepta- and 1 octa-isomers.

The physical properties of DBF and a few selected substituted DBFs are given in Table 1-1. As can be seen from Table 1-1, the physical properties of substituted DBFs are not well investigated. Alkyl or halogen substituted dibenzofurans are less polar and would be expected to be less soluble in water and more soluble in organic solvents. It is also expected that octanol/water partition coefficients for the alkyl and halogen substituted DBFs will be higher than the parent compound.

1.2. CHEMICAL PROPERTIES

Although DBF and its substituted compounds undergo a variety of chemical reactions, very few of these reactions appear to be environmentally significant. Dibenzofuran is relatively stable toward acid and alkali attack. The pyrolysis of DBF for 1.4 seconds in nitrogen at 0.6 atmosphere and 830°C caused only 4.5% decomposition. The products of decomposition are toluene, styrene, indene, durene, naphthalene, water, hydrogen, carbon, o-ethylphenol and polyphenyl ether. No decomposition is observed below 830°C (U.S. EPA, 1981).

TABLE 1-1

Physical Properties of Dibenzofuran and a Few Selected Substituted Dibenzofurans[a]

Compound	Melting Point (°C)	Boiling Point (°C)	Solubility in Water at 25°C	Octanol/Water Partition Coefficient	Calculated Vapor Pressure at 25°C	Specific Gravity	λmax, nm
DBF	82.8-83	276-287	3.1118 mg/L[b]	1527[b]	1.75×10^{-2}	1.0886 at 99°C	217, 245, 250, 280, 285, 295, 300 (in ethanol)
2-chloro-DBF	101-106	NR	NR	NR	NR	NR	NR
3-chloro-DBF	101	NR	NR	NR	NR	NR	NR
2,3-dichloro-DBF	125.5-127	NR	NR	NR	NR	NR	NR
2,8-dichloro-DBF	185	NR	NR	NR	6.8×10^{-6}	NR	290 (in methanol)
3,7-dichloro-DBF	186-188	NR	NR	NR	7.0×10^{-6}	NR	NR
1,2,3,4-tetrachloro-DBF	169-170	NR	NR	NR	NR	NR	NR
2,3,6,8-tetrachloro-DBF	202-203	NR	NR	NR	NR	NR	250, 260, 285, 297, 314 (in chloroform)
2,3,7,8-TCDF	226-228	NR	>0.2 µg/L[c]	NR	2.0×10^{-6}	NR	257, 294, 310, 323 (in chloroform)
2,4,6,8-TCDF	198-200	NR	NR	NR	2.5×10^{-6}	NR	259, 309, 316 (in chloroform)
Octachloro-DBF	NR	NR	NR	NR	0.19×10^{-6}	NR	NR
2-methyl-DBF	45	NR	NR	NR	NR	NR	NR

[a]Source: U.S. EPA, 1981

[b]For the tritiated compound

[c]Estimated value

The photolysis of CDBFs has been studied more extensively. The photodegradation of OCDF at 310 nm in n-hexane is more rapid than that of 2,8-dichlorobenzofurans. The half-lives were ≈1.5 and 2.5 hours, respectively (U.S. EPA, 1981). However, the rate of photolysis has a pronounced solvent dependency. For example, some experimental results provide indirect evidence that CDBFs in aqueous solution may be destroyed at 254, but only very slowly at 310 nm (U.S. EPA, 1981). The major products of photolysis of CDBFs are formation of polymer and dechlorinated products.

1.3. SYNTHESIS

The two important methods for the synthesis of DBF are thermal dehydration of 2,2'-dihydroxy-biphenyl and catalytic dehydrogenation of o-phenylphenol. Specific CDBFs have been synthesized by direct chlorination of DBF, photolysis of chlorinated diphenyl ethers, cyclization of substituted 2,2-dihydroxy biphenyls and photodechlorination of OCDF. The synthetic routes which have environmental implication are the thermal production of CDBFs from PCB isomers, polychlorinated diphenyl ethers and chlorobenzenes (U.S. EPA, 1981).

1.4. SOURCES IN THE ENVIRONMENT

Polychlorinated dibenzofurans occur as contaminants in a number of halogenated aromatics, namely, phenoxy herbicides, polychlorinated phenols, hexachlorobenzenes and PCBs. Polychlorinated dibenzofurans enter the environment during the release of these halogenated aromatics in industrial wastes or as disposed waste products from the manufacture of these chemicals (U.S. EPA, 1981).

The CDBFs and alkyl DBFs are also formed in the environment by photolytic and pyrolytic reactions from chlorinated chemical products. For example, DBF and alkyl DBFs are produced as combustion products of coal,

petroleum distillate, tobacco smoke and municipal refuse. It is photochemically produced from diphenyl ethers (U.S. EPA, 1981).

Complex DBFs can occur in alkoids, lichen products and some fruits. The DBFs have also been detected in volatiles of cotton plants and in dried fish (U.S. EPA, 1981).

1.5. USES

Dibenzofurans are used as intermediates in the manufacture of dyes, electrical insulation, fireproofing, fluorescent whiteners, herbicides, bactericides and medicines (U.S. EPA, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR, WATER AND SOIL

At present, very little is known about the environmental fate and transport processes of DBFs. However, based on the similarity of physicochemical properties of these compounds with the PCDDs, some predictions can be made about their environmental dynamics.

It has been reported that 2,3,7,8-TCDDs are fairly stable and immobile in soil. The dioxins are not transported by irrigation or rainfall and only small latent movements occur due to erosion. The apparent half-life of 2,3,7,8-TCDDs in soil was estimated to be 330 days for areas with dry climates and 190 days for areas with moist and warm weather (U.S. EPA, 1981). Based on these results, it can be predicted that the PCDFs will be persistent in soils.

The photochemical reactions of CDBFs were discussed in Section 1.2. It is difficult to extrapolate the static artificial systems to the photochemical fate of CDBFs in dynamic ecosystems. However, from the discussion in Section 1.2. and drawing analogy from PCDD photolysis it can be predicted that the CDBFs in aquatic media may be persistent toward photodegradation, since the wavelength of sunlight reaching the troposphere exceeds 290 nm.

The biodegradability of DBFs in soil and in aquatic environment has not been studied. If the biodegradation potential of CDBFs is assumed to be similar to 2,3,7,8-TCDD, the CDBFs are expected to show resistance towards microbial degradation in soil and in the aquatic environment.

2.2. BIOACCUMULATION

The accumulation of PCDFs in mallards was studied by feeding the ducks a diet contaminated with PCB containing 1.5 mg PCDFs/kg of PCB (U.S. EPA, 1981). After 1 year, lipid samples were analyzed for the presence of PCDFs

and PCB. It was concluded that no more than 3% of the dosed PCDFs was accumulated by the mallards. Although these data suggest a low bioaccumulation of PCDFs in birds, the bioaccumulation potential of these chemicals to aquatic organisms remains to be evaluated.

During experiments in a model ecosystem, DBF has been shown to bioaccumulate in Oedogonium cardiacum alga (82x), Physa sp. snail (2858x), mosquito larvae (2094x) and in Gambusia affinis fish (947x) (U.S. EPA, 1981). Polar metabolites comprised 69, 41, 25 and 14%, respectively, of the degradation products, while 40, 38, 27 and 30%, respectively, were nonpolar metabolites.

Carlson et al. (1979) conducted 28-day flowthrough bioconcentration experiments with fathead minnows (Pimephales promelas) and DBF in combination with other polynuclear aromatic hydrocarbons. The equilibrium 28-day BCF of dibenzofuran in whole fish (containing 4.6% lipid) ranged between 1100 and 1700. Equilibrium concentrations were reached after 2-4 days of exposure and >97% of the accumulated DBF was eliminated in 2 days.

Zitko and Choi (1973) and Zitko et al. (1973) provided the only available experimental data concerning bioaccumulation of CDBFs in fish. Zitko and Choi (1973) fed Atlantic salmon (Salmo salar) food spiked with a mixture of di-, tri-, tetra- and octachlorodibenzofuran. Only OCDF, at concentrations lower than in the food, could be detected in the fish. Zitko et al. (1973) also showed that only a small portion ($\leq$0.4%) of orally administered 2,8-dichlorodibenzofuran was accumulated in the tissues of brook trout (Salvelinus fontinalis). These results indicate that CDBFs are poorly absorbed in the gut of fish. Pertinent data regarding the bioconcentration from water of CDBFs by aquatic organisms were not located in the available literature.

The bioaccumulation factor of a chemical in a whole fish can be theoretically calculated from several equations. If the equation of Veith et al. (1979), namely, log BCF = 0.76 log octanol/water partition coefficient -0.70, and the octanol/water partition coefficient of $<2.04 \times 10^7$ [a value of 2.04×10^7 has been determined for 2,3,7,8-TCDD by Leo (1977)] is assumed for 2,3,7,8-TCDF, the BCF for this chemical in whole fish tissue would be $<7.2 \times 10^6$.

3. EXPOSURE

3.1. WATER

Trichlorodibenzofurans (isomers not identified) were detected in the wastewater of a chemical manufacturing plant and in the water of a river receiving the industrial wastewater (Jungclaus et al., 1978). No data, however, are available pertaining to the level of any DBFs in United States drinking waters.

3.2. FOOD

Both 2,3,7,8-tetrachlorodibenzofuran and 2,3,4,7,8-pentachlorodibenzofuran have been detected in fats from Hudson River snapping turtles and Baltic gray seals (U.S. EPA, 1981). The turtle fat was shown to contain 45 and 620 ppt of the two compounds, respectively. The respective levels in seal fat were 1 and 15 parts per trillion (ppt).

The level of DBFs in aquatic and other foods is unavailable, although Ribick et al. (1979) reported the presence of tetra-, penta-, hexa- and heptachlorodibenzofurans in fish collected from Ohio River water. The first three isomers were also detected in fish from Connecticut River and Lake Michigan waters. Fish collected from Hudson River water were reported to contain only hexachlorodibenzofuran. The United States dietary intake of 2,3,7,8-TCDF from fish consumption can be estimated indirectly. The present dietary intake of PCB from fish in the United States is ≈175 µg/day (U.S. EPA, 1981). If the amount of 2,3,7,8-TCDF in PCB is the same as found in Japanese Kanechlor 400 formulation (similar to Aroclor 1248) (i.e., 1.25 ppm), the amount of 2,3,7,8-TCDF consumption would be ≈0.2 ng/day.

Another source of DBFs in foods could be meat and poultry products. If these products contain PCB, some CDBFs may be formed as a result of pyrolysis of PCB during cooking. A level of 0.4 ppb hepta- and 0.4 ppb octa-

chlorodibenzofuran has been reported in 2 of 15 commercial United States gelatins (U.S. EPA, 1981). Ryan and Pilon (1980) reported the concentrations of OCDF in two chicken liver samples to be 87 and 130 pg/g.

In 1968, more than 1200 people in southwest Japan were intoxicated by consuming a commercial rice oil ("Yusho" oil) contaminated with PCBs and PCDFs. The contaminants were probably introduced into the oil during processing as a result of leakage from heat exchangers containing PCBs contaminated with PCDFs (IARC, 1978). Nagayama et al. (1976) analyzed the "Yusho" oil and detected 5 ppm PCDF, the major constituents of which were tetra- and penta-CDFs. Buser et al. (1978b) have recently shown that 2,3,7,8-TCDF was the main PCDF in the "Yusho" oil and its concentration was determined to be 0.45 pm.

It can be concluded from the above discussion that the monitoring data are insufficient for the estimation of United States dietary intake of DBFs from all foods.

3.3. AIR

Chlorinated dibenzofurans have been found as impurities in PCB, chlorophenols, chlorobenzenes and in some phenoxy herbicides. Therefore, the use of any of the latter chemicals will result in the atmospheric emission of some CDBFs. Pyrolysis of a technical grade PCB mixture yielded many PCDF isomers. The total yield could be as high as 3-25%. One of the main constituents of PCB pyrolysis is the tetra-isomer, the most toxic PCDF isomer (IARC, 1978). Consequently, unintentional burning of PCB, such as welding or soldering electrical equipment containing PCBs or using casting waxes in foundries, may possibly entail a significant exposure to PCDFs (Buser et al., 1978a). Another possible source of exposure of PCDFs is the burning of PCB-containing waste oils (IARC, 1978). A PCB (Kanechlor 400) used in a

heat exchanger system for 2 years contained ≈1.25 ppm TCDF and a total of 15 ppm PCDFs (Buser et al., 1978b). The level of PCBs in ambient air has been reported to be ≈100 ng/m^3 (U.S. EPA, 1981). If the ratios of TCDF and PCDFs to PCBs in the atmosphere are the same as found in Japanese Kanechlor 400, the concentration of TCDF and PCDFs in ambient air would be ≈0.1 and 1.5 pg/m^3, respectively.

The burning of both industrial and municipal wastes in incinerators, stack emissions, fly ash from coal refuse burning and electrical fires involving PCB insulation may produce halogenated benzofurans in the atmosphere (U.S. EPA, 1981). Recently, Buser and Bosshardt (1978) quantified PCDFs in fly ash from an industrial incinerator heating facility and a non-incinerator heating facility in Switzerland to be 0.1 and 0.3 ppm, respectively. A large number of PCDF isomers were detected in the fly ash, but the highly toxic isomers were found to be the major constituents (Buser et al., 1978c).

Under simulated environmental conditions, the combustion of a standard 2,4,5-T formulation led to formation of small amounts of PCDFs (Ahling et al., 1977). Therefore, workers manufacturing 2,4,5-trichlorophenol or 2,4,5-T during normal production operations and/or following explosions in these plants, may be exposed to PCDFs (IARC, 1978). Apparently, PCDFs are produced in the earlier stages of production processes when mainly tetrachlorobenzene is present and PCDDs are produced toward the end of the production processes when primarily trichlorophenol is present (IARC, 1978).

3.4. DERMAL

Pertinent data regarding dermal exposure to dibenzofurans were not located in the available literature.

4. PHARMACOKINETICS

4.1. ABSORPTION

Rats given 30.6 or 306 µg/kg of ^{14}C-2,3,7,8-tetrachlorodibenzofuran and guinea pigs given 6 µg/kg of ^{14}C-2,3,7,8-TCDF absorbed >90% of the administered dose (Birnbaum et al., 1980; Decad et al., 1981a,b). The chemical was administered orally to both species. No quantitative data for absorption of DBF or its chlorinated derivatives by humans or monkeys were presented in the multimedia criteria document for dibenzofurans (U.S. EPA, 1981).

4.2. DISTRIBUTION

The clearance and distribution of PCDFs in laboratory animals have been studied using mixtures of various isomers of tetra-, penta- and hexa-CDBF or using pure ^{14}C-labeled 2,3,7,8-TCDF. Morita and Oishi (1977) administered 0.5 mg of a mixture of PCDFs to ICR mice. Analysis of the mixture showed that it contained 2 tetra-, 4 penta- and 4 hexa-CDBFs. Liver and adipose tissue followed by the spleen were the main sites of disposition of PCDFs.

When administered in the diet to mice during pregnancy and lactation, PCDFs were accumulated in the dams' livers (5.1% of the total amount ingested) more than in other tissues. Transfer across the placenta was limited, being to only 0.003% of the total amount ingested by the dams. Transfer to the suckling offspring through the milk was pronounced and accounted for 1.2% of the total amount ingested. The PCDFs (a mixture of 48% tetra-, 49% penta- and 3% hexa-CDBFs) were administered at a concentration of 0.6 ppm in the diet for 18 days after mating and 14 days after delivery (Nagayama et al., 1980).

Kuroki et al. (1980) investigated the accumulation of PCDFs in the liver of rats and monkeys. They used the following mixture of PCDFs: 1,2,7,8-tetra (14%); 2,3,7,8-tetra (35%); 1,2,4,7,8-penta (1%); 1,2,3,7,8-penta (49%); 2,3,4,7,8-penta (1%); and unspecified hexa-CDBF (1%). Male Wistar rats were given a single i.p. dose of 10 mg of the mixture/kg. The animals were killed after 5 days. The 1,2,7,8-tetra- and 1,2,4,7,8-penta-CDBF compounds were not detected in the liver, while the 2,3,7,8-penta- and the hexa-CDBF were retained in the liver at ≈78 and 100%, respectively, of the total dose. In a related experiment, Kuroki et al. (1980) fed 0.25 or 0.50 mg/kg Kanechlor 400, together with 1.25 or 2.5 µg/kg of the PCDF mixture, to one male and two female rhesus monkeys for 26-32 days. The liver and adipose tissue retained more penta- and hexa-CDBFs than tetra-CDBFs; the 2,3,4,7,8-penta isomer was the most highly accumulated.

Birnbaum et al. (1980) administered radiolabeled 2,3,7,8-TCDF to rats orally (30.6 or 306 mg/kg) and i.v. (30.6 mg/kg) and found that, in both cases, the radioactivity was distributed initially to the liver (24% of the total administered dose) and muscle (25% of the dose) followed by some redistribution to adipose tissue and skin.

After administration of ^{14}C-2,3,7,8-TCDF to monkeys and rats, the radioactivity present in the tissues including the liver was the parent compound, with the exception of traces of metabolites in the blood. The radioactivity excreted from the body was in the form of metabolites (Birnbaum et al., 1980, 1981).

Guinea pigs given a toxic dose of ^{14}C-2,3,7,8-TCDF had high levels of radioactivity in liver, muscle, skin and adipose tissue (Decad et al., 1981a,b). The radioactivity began to redistribute from the adipose tissue

to the liver 1 day after administration; this phenomenon was associated with the mobilization of fat stores. Similar results were obtained by Gasiewicz and Neal (1979).

PCDFs have also been detected in humans. Rappe et al. (1981) reported levels of PCDFs in the blood of workers exposed to 2,3,4,6-tetrachlorophenol, and in workers exposed to pentachlorophenol laurate and pentachlorophenol. It was observed that the levels of PCDFs found in the blood correlated well with the amount of PCDFs in the original compound.

In 1968, ≈1200 people in southwest Japan consumed a commercial rice oil contaminated with high concentrations of PCBs and PCDFs. Measurable amounts of PCBs and PCDFs were found in some of these "Yusho" patients but not in patients with other diseases. The liver and adipose tissue of "Yusho" patients had approximately similar concentrations of PCDFs. Of the various isomers detected, the 2,3,4,7,8-penta-CDBF was found in the highest concentration (U.S. EPA, 1981). This compound was still detectable in a patient's tissues 9 years after ingestion of the contaminated rice oil (Kuroki and Masuda, 1978). According to Kuroki and Masuda (1978), patient number 3 ingested 16.8, 56-252 and 56 µg of 2,3,6,8-tetra-, 2,3,7,8-tetra- and 2,3,4,7,8-penta-CDBF, respectively. The liver contained 63.3, 15.8 and 565 ng of the three isomers; thus, 0.37, 0.006 and 0.9% of the respective isomers remained in the liver of the patient when he died 44 months later.

Rappe et al. (1979) have also reported the occurrence of various isomers in two patients who had eaten the contaminated rice oil. Most of the isomers identified had all lateral (2,3,7,8-) positions chlorinated.

4.3. METABOLISM

Guinea pigs given 6 µg/kg of ^{14}C-2,3,7,8-TCDF orally metabolized the chemical very slowly. This dose, however, is in the range of the LD_{50} for

this species. Only 6.6% of the administered radioactivity was excreted as metabolites in the urine (no metabolites were excreted in the feces) within 9 days, by which time the animals were moribund and had lost nearly half their total adipose tissue (Decad et al., 1981a,b). Rats metabolized ^{14}C-2,3,7,8-TCDF readily and had excreted more than half an orally administered dose of 30.6 or 306 µg/kg as metabolites in the feces and another 6% as metabolites in the urine within 2 days (Birnbaum et al., 1981). Monkeys appeared to be intermediate between the other two species in ability to metabolize ^{14}C-2,3,7,8-TCDF, judging from the excretion of metabolites in feces and urine (Birnbaum et al., 1981).

4.4. EXCRETION

Birnbaum et al. (1980) investigated the excretion of ^{14}C-2,3,7,8-TCDF in male Fischer rats after oral administration (30.6 or 306 µg/kg) or i.v. injection (30.6 µg/kg). They found that the primary route of excretion was via fecal elimination through the bile. Biliary excretion accounted for over 7% of the dose within 6 hours and 24% of the total dose was observed in the feces within the first day. Less than 6% of the total dose of the radioactively labeled compound was excreted in the urine, with >50% being excreted in the feces within 2 days following administration. It was estimated that the whole-body half-life of the compound was <2 days.

Morita and Oishi (1977) administered 0.5 mg of a mixture of PCDFs to mice (see Section 4.2. for details of experiment). They found that the less chlorinated compounds disappeared from the tissues faster than did the highly chlorinated ones. Clearance was slower from the liver than from the adipose tissue or spleen. The compound 2,3,7,8-TCDF seemed to have an approximate half-life of 1 week in the liver, while the entire mixture had a biological half-life of about 2 weeks.

Birnbaum et al. (1981) administered 30.6 µg/kg ^{14}C-2,3,7,8-TCDF i.v. to male rhesus monkeys. Both urinary and fecal routes of excretion were measured with the fecal route being 4 times greater than the urinary route. After 21 days, <10% of the labeled compound remained in the body. The whole body half-life of the compound was estimated to be ≈8 days.

Guinea pigs, after a (toxic) dose of 6 µg/kg of ^{14}C-TCDF, excreted the compound very slowly. Only 6.6% of the dose of radioactivity had appeared in the feces within the first 9 days and was excreted as parent compound; an additional 6.6% was excreted in the urine as metabolites (Decad et al., 1981a,b). The whole-body half-life of the compound, estimated during the period before severe toxicity was manifest, was ≈20 days.

5. EFFECTS

5.1. CARCINOGENICITY

According to the U.S. EPA (1981), the potential carcinogenicity of the halogenated DBFs has not been investigated and there is no direct experimental data to suggest that any of them may be carcinogenic. Because the PCDDs have biological effects similar to those of the PCDFs, the carcinogenic behavior of the PCDDs raises the suspicion that the closely-related PCDFs may also be carcinogenic.

As reported in the multimedia criteria document for the dibenzofurans (U.S. EPA, 1981), oral administration of 2,3,7,8-TCDD induced cancer in both rats and mice, while dibenzo-p-dioxin and 2,7-di-CDD did not. Other studies have shown that a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexa-CDD administered orally was carcinogenic in rats and mice. In addition, the compound 2,4,6-trichlorophenol, a phenol of known high PCDF and PCDD content, was found to be carcinogenic (U.S. EPA, 1981).

Several aminodibenzofurans and p-dimethylaminoazodibenzofurans have been reported to induce bladder tumors and carcinomas in laboratory animals. However, there are no reported experiments indicating any carcinogenic properties of unsubstituted DBF (U.S. EPA, 1981).

Epidemiologic studies of groups exposed to chemicals (such as PCBs and chlorophenols) known to be contaminated with PCDFs and PCDDs suggest an association between such exposure and an increased risk of cancer (U.S. EPA, 1981). The role of contaminants relative to the parent compounds cannot, however, be readily evaluated. Additional problems in interpretation arise from the lack of quantitative exposure data and the presence of other confounding factors.

5.2. MUTAGENICITY

Few studies have been reported on the capacity for DNA damage and mutation by DBF or its derivatives. Schoeny (1981) tested DBF, 2,3,7,8-TCDF and OCDF for mutagenicity to Salmonella typhimurium. When the vehicle was benzene:isooctane (1:9), none of the above compounds were mutagenic for any of the standard Salmonella test strains (namely, frameshift specific strains TA1538 and TA1537, the missense indicator TA1535, and the strains TA98 and TA100). The results were the same whether the DBFs were assayed in the absence or in the presence of hepatic metabolic activating systems prepared from rats treated with 2,3,7,8-TCDF or other enzyme-inducing agents. Similarly, 2,8- and 3,6-di-CDBF also gave negative results with the standard Salmonella typhimurium tester strains (Schoeny, 1981). Dose levels were limited by the low water solubilities of these chemicals and the toxicity of the non-polar solvent system that was used.

A mixture of PCDF isomers (apparently having 3-6 chlorines) was reported to markedly increase sister chromatid exchanges in Chinese hamster lymphocyte cultures (Inoue et al., 1979). 2,3,7,8-TCDF and OCDF gave negative results in the Bacillus subtilis rec assay which tests for DNA damage (Schoeny, 1981).

5.3. TERATOGENICITY

The literature searched failed to reveal any published reports of teratogenic studies of the CDBFs. However, there are a few teratogenic studies on materials assumed (or documented) to contain halogenated dibenzofurans as low-level contaminants. Review of these mammalian teratology studies gave no positive indication of a teratogenic effect associated with the lower level contamination in chlorinated phenols or PCBs (U.S. EPA, 1981).

Although the teratogenicity of the DBFs has not been evaluated, there are a few teratogenicity studies of dibenzodioxin homologs of DBFs. If the two categories of compounds have parallel effects as is suggested by their short-term toxicity, then based on the studies of dibenzodioxins there should be a wide variation in teratological properties of the CDBFs. Of the CDDs tested thus far, 2,3,7,8-TCDD and hexa-CDD were teratogenic to rats, but 2,7-di-CDD and octa-CDD were not (U.S. EPA, 1981).

5.4. OTHER REPRODUCTIVE EFFECTS

Sprague-Dawley rats were fed a mixture of 2 tetrachloro-, 4 pentachloro- and 4 hexachloro-isomers of DBF at levels of 0, 1 and 10 ppm in the diet. The 10 ppm dose level significantly decreased the testosterone levels in the testes; the decrease elicited by the 1 ppm dose was not significant. Seminal vesicle and ventral prostate weights were significantly reduced by the 10 ppm dose (Oishi et al., 1978).

Twelve of 13 babies born to women who ingested 0.3-2.6 g of "Yusho" oil (rice oil contaminated with PCBs and PCDFs) during pregnancy were smaller than the national average and 10 had grey and dark brown pigmentation of the skin, a condition which was still occurring in babies born to parents 3 years after severe exposure to the oil. This pigmentation was also reported in the gums and nails. In 9 of 13 newborns, heavy eye discharge occurred. There have also been reports of developmental abnormalities, including premature tooth eruptions (two cases), larger frontal and occipital fontanelles, exophthalmus and persistent abnormally wide sagittal suture (three cases) (U.S. EPA, 1981).

5.5. CHRONIC TOXICITY -- HUMANS

The available information on the effects of DBFs on humans comes mostly from Japan, where in 1968 many people ate rice oil that was later found to

be contaminated with PCBs and PCDFs. The contamination occurred via leakage from a heat exchanger containing Kanechlor 400. Because this incident has been extensively reviewed (Kuratsune et al., 1976; Kimbrough, 1974; WHO, 1976, 1978; CNRC, 1978), only an overview of clinical effects was presented by the U.S. EPA (1981) and can therefore be summarized here.

The U.S. EPA (1981) presented no data pertinent to the duration of exposure, but according to Deichmann (1981) the victims of "Yusho" poisoning had ingested contaminated rice oil for "several months." Symptoms of intoxication appeared after a latent period of 5-6 months (Deichmann, 1981) and continued over a period of years (Urabe et al., 1979).

The number of people who ingested the contaminated rice oil does not appear to be known. The number of poisoning cases was variously reported to be 1057 in 1972 (Kuratsune et al., 1972) and 1665 in 1975 after new diagnostic criteria were adopted (Urabe et al., 1979). Symptoms and signs observed in 189 persons with "Yusho" disease are listed in Table 5-1, along with the percentage of patients affected. According to Deichmann (1981), the contaminated rice oil was considerably more toxic than would be expected from the concentrations of PCBs it contained, leading to the suspicion that the highly toxic PCDFs were also present. This suspicion was confirmed in 1975-1976, when Nagayama et al. (1976) found that PCDFs were present in the Kanechlor 400 involved in the poisoning episode at concentrations many times higher than those present in freshly manufactured Kanechlor 400. Samples of the same rice oil that had been consumed were found to contain 1000 ppm PCBs and 5 ppm PCDFs, with major PCDF components being the tetra- and pentachlorinated isomers.

Rough estimates linking the amount of rice oil consumed (and, hence, quantities of PCBs and PCDFs) to the severity of clinical findings are available for a limited number of cases. These data are shown in Table 5-2.

TABLE 5-1

Symptoms of "Yusho" Disease in 89 Male and 100 Female Patients*

Symptoms	Males (%)	Females (%)
Blackening of nails	83.1	75.0
Black spots in all pores	64.0	56.0
Excessive sweating in palms	50.6	55.0
Acnelike skin eruptions	87.6	82.0
Red spots on limbs	20.2	16.0
Itching	42.7	52.0
Change in skin color	75.3	72.0
Swelling of hands and feet	20.2	41.0
Hardening of backs and hands	24.7	29.0
Pigmentation of mucous membranes	56.2	47.0
Sebum (gum secretion in eyes)	88.8	83.0
Hyperemia of mucous membranes in eyes	70.8	71.0
Temporary failing of eyesight	56.2	55.0
Jaundice	11.2	11.0
Swelling of upper eyelids	71.9	74.0
Sense of weakness	58.4	52.0
Numbness of hands and feet	32.6	39.0
Fever	16.9	19.0
Hearing difficulty	18.0	19.0
Spasms of hands and feet	7.9	8.0
Headaches	30.3	39.0
Vomiting	23.6	28.0
Diarrhea	19.1	17.0

*Source: U.S. EPA, 1981 (derived from Kuratsune et al., 1972)

TABLE 5-2

Relation Between the Amount of the Rice Oil Used by "Yusho" Patients, Amounts of PCB and PCDF Ingested, and Clinical Severity[a]

Amount of Rice Oil (mℓ)	Consumed[b] PCB (g)	Consumed[b] PCDF (mg)	Nonaffected	Light Cases	Severe Cases	Total
<720	<0.7	<3.6	10 (12.0)[c]	39 (49.0)	31 (39.0)	80
720-1440	0.7-1.4	3.6-7.2	0	14 (31.0)	31 (69.0)	45
>1440	>1.4	>7.9	0	3 (14.0)	18 (86.0)	21

[a]Source: U.S. EPA, 1981 [derived from Kuratsune et al. (1972) and Nagayama et al. (1976)]

[b]Calculated on the basis of the concentrations of PCB (1000 ppm) and PCDF (5 ppm) found in the contaminated rice oil by Nagayama et al. (1976).

[c]Percentage of cases is given in parentheses.

In addition to the signs and symptoms listed in Table 5-1, various clinical, biochemical and histological abnormalities have been reported in "Yusho" patients. Diagnostic tests for liver function and damage indicated slight rises in serum transaminases and alkaline phosphatase, and occasionally low bilirubin levels. Examination of a liver biopsy specimen taken from one exposed individual revealed a marked proliferation of smooth endoplasmic reticulum. Also reported were unspecified liver enlargement and disturbances. Plasma cholesterol and phospholipid levels were always normal, but serum triglycerides increased to 4 times the normal value. In 38 patients, 2 years after the accident, there remained a lower than normal immunoglobulin level and, in some of the patients, an increased excretion of α-ketosteroid (U.S. EPA, 1981). Strik (1979) found no alteration in porphyrin metabolism in "Yusho" patients or other manifestation of porphyria cutanea tarda.

As stated in the document on dibenzofurans (U.S. EPA, 1981), Urabe et al. (1979) summarize well the limited information available on an undefined portion of the affected population and the sequence of appearance of manifestations of the disease:

> At the beginning of the outbreak, lesions that led to the diagnosis of "Yusho" were mainly limited to the skin and mucous membranes. They included black comedone and acneform eruptions, pigmentation of the face, eyelids, gigivae and nails, hypertrophy of the Meibomian glands, and hypersecretion from the eyes. In addition to these mucocutaneous manifestations, systemic signs, such as loss of appetite, nausea, vomiting, weakness, and numbness of the extremities were also reported; but at that time these were regarded as complications of minor importance. During the 6 years from 1969 to 1975, the mucocutaneous lesions improved in 64% of the patients. These lesions gradually gave way to systemic disorders, such as dullness, headache or heavy-headedness, indefinite stomachache, numbness or pain of the extremities, swelling and pain of the joints, coughing, and bronchitis-like symptoms. Children showed retarded growth and abnormal tooth development; newborn babies were underweight and showed systemic pigmentation. These changes of the clinical diagnostics therefore compelled researchers to alter the criteria for diagnosis in 1973. A new technique developed for

determining blood PCB levels made it possible to establish more accurate criteria for diagnosis of "Yusho", and to delve into various contributory findings, including increased blood levels of triglycerides, anemia, lymphocytosis, hypoalbuminemia, adrenocortical hypofunction, and reduction of sensory nerve conduction velocity.

The multimedia criteria document for the dibenzofurans (U.S. EPA, 1981) did not cite any chronic toxicity studies on DBFs. A summary of the subchronic toxicity of PCDFs to experimental animals is presented in Table 5-3.

Oishi et al. (1978) reported that male Sprague-Dawley rats fed 10 ppm (0.5 mg/kg bw/day) of CDBF in the diet (an unspecified mixture of 2 isomers of tetra-CDBF, 4 isomers of penta-CDBF and 4 isomers of hexa-CDBF) for 4 weeks lost weight and developed chloracne-like lesions on the ears, reduced thymus, ventral prostate and seminal vesicle weights, low hematocrit and hemoglobin values, increased serum cholesterol and liver lipids, and low serum triglycerides. These effects were less marked at 1 ppm in the diet.

Clinical signs of toxicity did not develop in mice given 22 oral doses over 30 days of 30, 100 and 300 µg/kg 2,3,7,8-TCDF (Moore et al., 1979). Absolute and relative liver weights were elevated, but relative thymus weights were markedly reduced.

McNulty et al. (1961) reported that 2,3,7,8-TCDF caused some deaths and sickness in two groups of three rhesus macaques each fed for 2 and 6 months with 50 and 5 µg/kg (i.e., ppb) of the compound in their food, respectively. Actual intake of the compound, based on food consumption, was 5 and 0.5 µg/kg bw/day for the two different dietary concentrations. The main pathological changes were atrophy or squamous metaplasia of the sebaceous glands, involution of the thymus and hypoplasia of the bone marrow. Survivors appeared to recover completely after 3 months of a 2,3,7,8-TCDF-free diet.

TABLE 5-3

Subchronic Toxicity of Polychlorinated Dibenzofurans[a]

Compounds	Species	Dose (µg/kg/day)	Mortality (%)	Route	Clinical Pathology	Reference
2 isomers-tetra-CDBF 4 isomers-penta-CDBF 4 isomers-hexa-CDBF	rat S.D.[b]	50 (28 days) 500 (28 days)	none none	1 ppm 10 ppm diet	Thymic involution; dermal lesions; hypercholesterolemia; hyperlipidemia; hemolytic anemia thrombopenia	Oishi et al., 1978
2,3,7,8-tetra-BDBF[c] 2,3,4,7,8-penta-CDBF 2,3,7,8-tetra-CDBF	mouse C57Bl	30-300 (30 days)	none	gavage	Thymic involution; hepatomegaly	Moore et al., 1979
PCDF	mouse	50 (10 weeks)	none	0.6 ppm diet	Dermal lesions; hyperkeratosis; dilated hair follicles with keratinous material; damaged hepatocytes	Nagayama et al., 1979
2,3,7,8-tetra-CDBF	adult rhesus macaque (3)	0.5 (6 months) 5 (2 months)	67 33	5 ppb 50 ppb diet	Atrophy or squamous metaplasia of sebaceous glands; mucous metaplasia and hyperplasia of the gastric mucosa; induction of the thymus; hypoplasia of the bone marrow	McNulty et al., 1981
2,3,7,8-tetra-CDBF	mature male guinea pig (4)	1 µg/kg/wk (6-7 weeks)	50	oral intubation	Bald patches, dehydration, swelling around eyes; no hepatomegaly	Decad et al., 1981b
2,3,7,8-tetra-CDBF	immature female guinea pig	1 µg/kg/wk (6 weeks)	30	oral intubation	Hepatomegaly and thymic atrophy	Luster et al., 1979a

[a]Source: U.S. EPA, 1981

[b]S.D. = Sprague-Dawley

[c]Tetrabromodibenzofuran

Guinea pigs were more sensitive to CDBF than were other species. Administration of only 1 µg/kg bw of 2,3,7,8-TCDF by intubation to guinea pigs once a week for 6-7 weeks resulted in 30-50% mortality (Decad et al., 1981b; Luster et al., 1979a). According to the U.S. EPA's (1981) review, depression of cell-mediated immune responses was observed in the guinea pigs, but only at high dosage levels (0.5-1 µg/kg/week), and humoral immunity was slightly depressed (Luster et al., 1979a). An abstract of another Luster et al. (1979b) paper indicates that doses as low as 0.05 µg/kg/week for 6 weeks were tested and found to be without effect. This data was not presented in the U.S. EPA (1981) document, and because the original paper is not readily available, cannot be confirmed as of this writing.

5.6. ACUTE

Rabbits given mixtures of tri- and tetra-CDBF orally at doses of 0.4 and 1 mg/kg bw developed severe liver necrosis that often proved fatal (Bauer et al., 1961). Rats, on the other hand, showed no signs of toxicity and had no tissue abnormalities after as much as 1 mg/kg of 2,3,7,8-TCDF (Moore et al., 1976). No deaths occurred among mice given single oral or s.c. doses of 2,3,7,8-TCDF up to 6000 µg/kg bw (Moore et al., 1976). The oral LD_{50} (30 days) for a mixture of 42% tetra-, 54% penta- and 4% hexaCDBF in CF_1 mice was reported to be 184 mg/kg for males and 414 mg/kg for females (Nishizumi, 1978).

Moore et al. (1979) report that the guinea pig is the that is most sensitive species to PCDFs, PCBs and PCDDs. The oral LD_{50} for 2,3,7,8-TCDF in guinea pigs was 5-10 µg/kg; no guinea pigs died at 5 µg/kg but all died at 10 or 15 µg/kg within 9-16 days (Moore et al., 1979). Toxic effects that occurred in the animals given 10 or 15 mg/kg included severe weight loss, atrophy of the thymus and spleen, debilitation of the lymphatic

system, hemorrhage of the adrenals and urinary bladder, and single-cell necrosis in the liver. Histologic examination of tissues revealed loss of lymphoid cells in the cortex of the thymus and epithelial hyperplasia in the renal pelvis, ureter and urinary bladder. Single doses of 5 or 1 µg produced weight loss or a decreased rate of weight gain in guinea pigs during the 30-day observation period, but no consistent or severe histological alterations at the end of 30 days (Moore et al., 1979). Moore et al. (1979) found no significant difference in acute toxicity between 2,3,7,8-TCDF 2,3,4,7,8-penta-CDBF and 2,3,7,8-tetra-BDBF.

McKinney and McConnell (1980) reported that the oral LD_{50} for 2,3,4,6,7,8-hexa-CDBF in Hartley strain guinea pigs was 120 µg/kg. The guinea pigs were observed for 30 days after administration of the chemical.

In a study done by McConnell and McKinney (1978), the toxicities of certain halogenated dioxins, dibenzofurans, biphenyls and naphthalenes in guinea pigs were compared. The most toxic isomers of each class of compounds were those in which at least three of the four 2,3,7,8 lateral positions of the aromatic nuclei were halogenated and at least one of the peri-positions was not. For the 30-day LD_{50}, the relative toxicity was: dibenzodioxin > dibenzofuran > biphenyl = naphthalene. All these compounds produced similar signs of toxicity, lesions and median time to death.

Moore et al. (1979) investigated the acute toxicity of 2,3,7,8-TCDF in the female rhesus monkey. Two monkeys given 1.5 mg/kg of 2,3,7,8-TCDF died 14 and 23 days after receiving the compound. Two of four monkeys died 25 and 31 days after receiving 1 mg/kg of the compound. The toxic effects were dose related. Signs of toxicity became detectable by 7-10 days after administration. Findings included mild anemia, reduced serum cholesterol,

moderate reduction in serum protein and albumin, neutrophilia, mild lymphopenia, and terminal increase in SGOT and BUN. The major gross and microscopic findings are summarized in Table 5-4.

Administration of 30.6 µg/kg 2,3,7,8-TCDF i.v. to three male rhesus monkeys resulted in characteristic lesions including alterations of the Meibomian glands and keratinaceous deposits in their ducts, and squamous metaplasia of the subaceous glands and of the ceruminous glands of the external auditory canal (Birnbaum et al., 1981). This dose is well below the LD_{50} for monkeys.

Birnbaum et al. (1980, 1981) and Decad et al. (1981a,b) compared toxicity and elimination of 2,3,7,8-TCDF in the guinea pig, monkey and rat. The severity of the toxic effects appeared to be inversely related to the ability of these three species to metabolize and excrete the parent compound. Rats, with a "whole-body half-time" of <2 days, experienced few acute toxic effects. In contrast, the guinea pig was extremely sensitive to the compound and had a "whole-body half-time" of ≈20 days. The monkey was intermediate in sensitivity and had a "whole-body half-time" for the compound of ≈8 days.

The acute oral toxicity of PCDFs for several animal species is summarized in Table 5-5. The related compounds 2,3,7,8-tetra-BDBF and 2,3,7,8-TCDD are included for the sake of comparison.

5.7. OTHER RELEVANT INFORMATION

The PCDFs can produce chloracne in man by either external contact with the chemical or by systemic absorption. Chloracne is a condition consisting of the formation of comedones with or without cysts and pustulas. The follicular orifices become filled with sebaceous and keratinous material.

TABLE 5-4

Summary of Pathologic Effects of 2,3,7,8-Tetra-CDBF in Rhesus Monkeys*

Tissue	Gross Effects	Microscopic Effects
Skin and adnexa	Facial edema, dry skin, loss of eyelashes, loss of finger and toe nails, streaks on ocular surface of eyelids, and occlusion of external ear canal	Hyperkeratosis; squamous metaplasia, cystic dilation of glands
Fat	Moderate to severe loss	None
Lymphoid	None	Atrophy-thymus due to lymphoid cell loss. Atrophy-moderate in lymphoid cells in spleen and lymph nodes
Liver	None	None
Bile duct	Markedly thickened	Hypertrophy of biliary duct and gall bladder epithelium, increased mucous secretion
Intestine	Hyperemia, petechial hemorrhage, focal ulceration and mucosal cysts	Loss of parietal cells, microscopic dilation of crypts

*Source: Adapted from U.S. EPA, 1981 (derived from Moore et al., 1979)

TABLE 5-5

Acute Oral Toxicity of Polychlorinated Dibenzofurans and 2,3,7,8-Tetra-CDD*

Compound	Species	LD_{50} (µg/kg)	Time to Death (days)	Clinical Pathology	Reference
2,3,7,8-tetra-CDF	guinea pig	>5 <10			
2,3,4,7,8-penta-CDF		>5 <10	9-20	Loss of body fat, atrophy of the thymus, loss of lymphoid cells, hyperplasia of epithelial cells in the renal pelvis, ureter, and urinary bladder; adrenal hemorrhage	Moore et al., 1979
2,3,7,8-tetra-BDF		>5 <10			
2,3,7,8-tetra-CDD	guinea pig	2	17-20		McConnell et al., 1978b
2,3,7,8-tetra-CDF	rhesus monkey	1000	14-31	See Table 5-4	Moore et al., 1979
2,3,7,8-tetra-CDD	rhesus monkey	<70	15-34		McConnell et al., 1978a
Mixture of 42% tetra-CDF, 54% penta-CDF, and 4% hexa-CDF	mouse (male)	200,000	15	Atrophy of the thymus, hepatomegalia, ascites, edema	Nishizumi, 1978
	mouse (female)	400,000			
2,3,7,8-tetra-CDD	mouse (female)	283	22-25		McConnell et al., 1978b
Mixture of tri-CDF and tetra-CDF	rabbit	500-1000	--	Severe liver necrosis	Bauer et al., 1961
2,3,7,8-tetra-CDF	rat	>6000	--	Mild toxic effect	Moore et al., 1976
	mouse				
2,3,4,6,7,8-hexa-CDF	guinea pig	120	--	Atrophy of thymus, debilitation of lymphatic system	McKinney and McConnell, 1980

*Source: Adapted from U.S. EPA, 1981

Other fairly common findings include hyperkeratosis of the epidermis, cystic dilation of the hair follicles and an increase in melanin pigment; these findings have been described in the appropriate toxicity sections.

Bauer et al. (1961) reported that application of a mixture of tri- and tetra-CDBF to the rabbit ear resulted in hyperplasia and hyperkeratosis. Similar results were reported by Vos and Beems (1971) with the application of a 25% diethylether-extracted polar fraction of Phenoclor and Clophen (which was identified as consisting of tetra- and penta-CDBF) to rabbit skin.

Nishizumi (1978) reported that tetra- and penta-CDBF induced hyperkeratosis of the skin when applied to rabbit ear for 3 days. Kimbrough et al. (1978) reported similar findings when daily doses of 4 µg 2,3,7,8-TCDF were applied to the rabbit ear for 5 days. Hairless mice fed rice oil contaminated with Kanechlor 400 developed hyperkeratosis (Inagami and Koga, 1969). Chloracne-like ear lesions were reported within 3 weeks in Sprague-Dawley rats fed a mixture of 2 tetra-, 4 penta- and 4 hexa-CDBF (Oishi et al., 1978) at a level of 10 ppm PCDFs in the diet and in mice fed 0.6 ppm PCDFs in the diet (Nagayama et al., 1979).

PCDFs have been found to be potent inducers of hepatic microsomal monooxygenases, and particularly of those monooxygenases that are inducible by 3-methyl-cholanthrene (U.S. EPA, 1981). As little as 0.1-2.5 µg/kg/day of 2,3,7,8-TCDF administered to rats for 3 days was effective in inducing these enzyme activities (Goldstein et al., 1978). A number of studies indicate that the PCDF isomers that are the most toxic are also the most potent inducers of monooxygenases (3-methylcholanthrene type). The PCDFs do not appear to have porphyrogenic effects (U.S. EPA, 1981).

6. AQUATIC TOXICITY

6.1. ACUTE

Acute toxicity information was found for one species of aquatic invertebrate and two species of fish. The 24- and 48-hour LC_{50} values of DBF to freshwater cladocerans (Daphnia magna) were 7500 and 1700 µg/ℓ, respectively (LeBlanc, 1980). The no-observed-effect concentration was 280 µg/ℓ. Zitko et al. (1973) reported that brook trout (Salvelinus fontinalis) were not affected by a single oral dose of 2,8-dichlorodibenzofuran at 122 mg/kg. The only study concerning acute toxicity to saltwater fish was that of Heitmuller et al. (1981) who reported that the 72- and 96-hour LC_{50} values of DBF to sheepshead minnows (Cyprinodon variegatus) were 3100 and 1800 µg/ℓ, respectively. The no-observed-effect concentration was 1000 µg/ℓ.

6.2. CHRONIC

Information concerning chronic toxicity was found for one species of saltwater invertebrate and two species of freshwater fish. Fingermann and Fingermann (1977) investigated the effects of 1,2,3,4,5,6,7,8-OCDF on the rate of molting of fiddler crabs (Uca pugilator) over a 38-day exposure period. Groups of crabs which were induced to molt by removal of four walking legs or both eyestalks were exposed to a nominal concentration of 16×10^{-10} (0.016 µg/ℓ) OCDF in artificial seawater or to uncontaminated medium. The cumulative percent molting in treated crabs was decreased by 11% in crabs without walking legs and by 23% in crabs without eyestalks, relative to the respective controls. The statistical significance of these differences could not be determined from the data provided. In addition, it was not specified whether control mortality occurred due to the removal of legs or eyestalks.

Zitko and Choi (1973) fed a group of 35 juvenile Atlantic salmon (Salmo salar) several times daily for 140 days with dry fish food spiked with a mixture of di-, tri-, tetra- and octachlorodibenzofuran. The measured concentration of each compound in the feed was 2.1, 4.4, 2.2 and 9.7 µg/g, respectively. Control fish fed with uncontaminated feed suffered no mortality. The median lethal time (LT_{50}) for exposed fish was 120±30 days. Mortality in the exposed group reached 80% by the end of the 140-day exposure period.

Zitko et al. (1973) also conducted long-term feeding experiments with immature brook trout (Salvelinus fontinalis) using 2,8-di-CDBF in gelatin capsules. No toxic effects were observed in fish administered with a cumulative dose of 107-361 µg 2,8-di-CDBF/g fish weight over an exposure period of at least 100 days.

6.3. PLANT EFFECTS

Pertinent data regarding toxicity to plants of DBFs and CDBFs were not located in the available literature.

6.4. RESIDUES

The equilibrium BCF of dibenzofuran in whole fathead minnows (Pimephales promelas) ranged between 1100 and 1700 (Carlson et al., 1979). Zitko and Choi (1973) reported that only octadibenzofuran was detected in Atlantic salmon (Salmo salar) fed a mixture of di-, tri-, tetra- and octadibenzofuran. Only a small portion (≤0.4%) of orally administered 2,8-dichlorodibenzofuran was accumulated in tissues of rainbow trout, Salvelinus fontinalis (Zitko et al., 1973).

Dibenzofuran and chlorinated dibenzofuran have been found in wild aquatic organisms. Dibenzofuran was detected but not quantified in fish samples from two rivers (Veith et al., 1981). Unspecified concentrations of CDBFs

have also been reported in fish samples from three rivers and Lake Michigan (Dougherty et al., 1980). Lake et al. (1981) measured 2,4,8-trichlorodibenzofuran residues in mussels and lobster taken from Naragansett Bay which is known to be polluted by this chemical (Jungclaus et al., 1978). Residue concentrations, based on dry tissue weight, were 1260 µg/kg in lobster hepatopancreas and 52-1180 µg/kg in mussels.

6.5. OTHER RELEVANT INFORMATION

A human odor threshold of 120 µg/ℓ of water has been established for unsubstituted dibenzofuran (U.S. EPA, 1975).

7. EXISTING GUIDELINES AND STANDARDS

Currently there appear to be no guidelines or standards for dibenzofuran or for any of its halogenated or other derivatives (U.S. EPA, 1981).

An ambient water criterion for 2,3,7,8-TCDD (an analog of CDBF) has been recommended by the U.S. EPA (1979) based on the carcinogenicity of the compound to experimental animals. The level of 2,3,7,8-TCDD in ambient water estimated to correspond to an upper limit estimate of increased lifetime cancer risk for humans of 10^{-5} was 2.1×10^{-9} µg/ℓ.

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